Internship Proposal

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Proposal At: 2024-01-12

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Project Title:
ToxicMuscle: an unusual model to approach repair in muscle disorders
Level:

Master Student

Project Summary:

CONTEXT: Damage to the plasma membrane (PM) occurs in healthy muscle cells due to mechanical tearing, as well as in dystrophic muscles due to aberrant expression or absence of PM repair proteins. We have uncovered a key player, the endoplasmic reticulum chaperone Gp96, that is involved in repairing PM damage induced by pore-forming toxins secreted by highly pathogenic bacteria. These toxins are simple to manipulate and cause reproducible and easily controlled damage in any cell type, intrinsic properties that make them valuable tools in fields of research other than infectiology. We propose that studies on PM damage induced by these toxins are of great value to identify new players and signalling pathways that can be modulated to promote PM repair in the muscle.
AIM: The goal here is to demonstrate that Gp96 and other proteins promoting PM repair upon toxin-induced damage are also involved in muscle repair upon mechanical damage.

Work to be developed by the student:

This project will include the following tasks and methodologies:
1)Deplete Gp96 (and related proteins involved in PM repair) in human muscle cells, or possibly establish muscle cell lines stably depleted of those proteins (by siRNA or CRISPR/Cas9 technology, lentiviral transduction)
2)Evaluate muscle cell resistance to PM damage induced by microinjuries in those cells expressing or not Gp96 (by immunofluorescence, light and electron microscopy).
This approach should provide proof-of-concept that PFT-induced damage is a relevant model to identify the machinery and pathways involved in muscle repair. Eventually, the impact of Gp96 and related proteins in PM repair can be validated in well-established and relevant muscular dystrophy animal models (like zebrafish).

References:

1.Mesquita FS, Brito C, Mazon Moya MJ, Pinheiro JC, Mostowy S, Cabanes D, Sousa S. "Endoplasmic reticulum chaperone Gp96 controls actomyosin dynamics and protects against pore-forming toxins." EMBO Rep. (2017) 18:303-318. DOI: 10.15252/embr.201642833.

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